

I. STUDIES ON THE *i*-STEROID REARRANGEMENT

II. RING ENLARGEMENT OF PYRROLE TO
3-SUBSTITUTED PYRIDINES

BY

AARON BROWN HERRICK

A.B., Princeton University, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
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I. STUDIES ON THE *i*-STEROID REARRANGEMENT

INTRODUCTION

The rearrangement of cholesteryl *p*-toluenesulfonate to 6 β -methoxy-3,5-cyclocholestane when treated with methanol and potassium acetate, and similar rearrangements of other Δ^5 -3 β -stenols to the ethers and esters of 3,5-cyclo-6 β -stanols is called the *i*-steroid rearrangement. The stereospecific and reversible rearrangement has been employed extensively to "protect" the C₅-C₆ double bond in the sterol molecule during synthetic and degradative operations on other parts of the molecule. The purpose of this investigation was to determine the applicability of the *i*-steroid rearrangement to acyclic sterol models.

DISCUSSION OF RESULTS

The first sterol analog investigated was 3-buten-1-ol, which was prepared from allylmagnesium bromide and formaldehyde. The *p*-toluenesulfonate of this γ,δ -unsaturated alcohol was subjected to acetolysis by means of two different acetolysis procedures and in each case the only compound isolated was 3-butenyl acetate rather than the desired cyclopropylmethyl acetate. The introduction of alkyl substituents in the δ -position of 3-buten-1-ol should afford compounds more favorably constituted for the rearrangement to occur, since it has been shown that the *i*-steroid rearrangement proceeds *via* a carbonium ion intermediate (1), and because the intermediate ion in this reaction would be a tertiary carbonium ion.

The synthesis of 4-methyl-3-penten-1-ol has been reported twice previously (2,3), but neither of the methods employed appeared to constitute an unequivocal synthesis of this compound. An unequivocal synthesis of 4-methyl-3-penten-1-ol was accomplished by the following procedure: 4-Methyl-2-pentenoic acid, prepared by the reaction between isobutyraldehyde and malonic acid, was heated with a 25% aqueous solu-

tion of potassium hydroxide, yielding a mixture of unsaturated acids (4), which when brominated afforded 3,4-dibromo-4-methylpentanoic acid. Esterification with diazomethane followed by debromination with zinc and methanol yielded methyl 4-methyl-3-pentenoate, which was converted to 4-methyl-3-penten-1-ol by reduction with lithium aluminum hydride. For comparison purposes, 2,3-dibromo-4-methylpentanoic acid, methyl 4-methyl-2-pentenoate, and 4-methyl-2-penten-1-ol were prepared. In every case, a decided difference in physical properties and infrared spectra indicated that the synthesis of 4-methyl-3-penten-1-ol was unequivocal.

Previous attempts to prepare 4-methyl-3-penten-1-ol from ethyl 4-chloro-4-methylpentanoate, 4-methylpentane-1,4-diol, and from 4-methylpentane-1,4-diol 1-monoacetate were unsuccessful. Ethyl 4-chloro-4-methylpentanoate, obtained by treating γ -methyl- γ -valerolactone with thionyl chloride followed by ethanolic hydrogen chloride, did not yield the desired ethyl 4-methyl-3-pentenoate when subjected to a number of dehydrohalogenation procedures. Dehydration of 4-methylpentane-1,4-diol gave 2-methyl-2,4-pentadiene rather than the expected unsaturated alcohol. Mixtures of products were obtained upon dehydration of 4-methylpentane-1,4-diol 1-monoacetate with iodine or oxalic acid.

The acetolysis of the *p*-toluenesulfonate of 4-methyl-3-penten-1-ol yielded the normal displacement product, 4-methyl-3-pentenyl acetate, in 96% yield. The infrared spectrum of this acetolysis product was identical with the spectrum of authentic 3-pentenyl acetate.

Based on the observed non-rearrangement of these acyclic sterol analogs when subjected to the conditions of the *i*-steroid rearrangement, it appears that steric factors play an important role in the *i*-steroid rearrangement, and it can be tentatively concluded that only cyclic sterol models will undergo this rearrangement.

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II. RING ENLARGEMENT OF PYRROLE TO
3-SUBSTITUTED PYRIDINES

INTRODUCTION

The ring enlargement of pyrrole to 3-chloropyridine was reported in 1881 (1). Subsequently, substituted pyrroles and indoles were also found to undergo the ring enlargement reaction with a number of substituted dihalomethanes in the presence of a variety of basic catalysts. The purpose of this investigation was to conduct an intensive study of the ring enlargement of pyrrole to 3-substituted pyridines in the hope that this reaction could be developed into a preparative method.

DISCUSSION OF RESULTS

The organometallic combinations utilized in this investigation were pyrrolyllithium (1), pyrrolylpotassium (2), and pyrrolysodium (3). The substituted dihalomethanes employed were chloroform, bromoform, benzal chloride and methylene iodide. The reaction between pyrrolyllithium, prepared from pyrrole and phenyllithium, and chloroform proceeded in 12.8 percent yield. Bromoform afforded 3-bromopyridine in 8.6 percent yield, while 3-phenylpyridine was obtained from pyrrolyllithium and benzal chloride in only 1.3 percent yield.

No pyridine was obtained from pyrryllithium and methylene iodide.

The reaction of substituted dihalomethanes with pyrrylsodium in ethanol or in a sealed tube resulted in the formation of 3-substituted pyridines in extremely low yields. The reaction of methylene iodide and pyrrylsodium in a sealed tube yielded a small amount of pyridine. Under no other reaction conditions was this result obtained. Pyrrylpotassium and chloroform yielded 3-chloropyridine in 7.2 percent, while no product was obtained when chloroform was allowed to react with pyrrylmagnesium bromide.

The purity and chemical constitution of the products of these ring enlargement reactions were determined by comparison with authentic 3-substituted pyridines. The 3-phenylpyridine was prepared by coupling diazotized 3-aminopyridine with benzene, while the 3-halopyridines were prepared by Sandmeyer reactions (4).

As a result of this investigation it can be concluded that the ring enlargement of pyrrole cannot be considered a satisfactory preparative route to 3-substituted pyridines.

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VITA

The author was born on May 20, 1924, in Wilkes-Barre, Pennsylvania, and received his elementary and secondary school education in Tunkhannock, Pennsylvania. Upon graduation from Tunkhannock High School in 1942, he attended the Gilman Country School in Baltimore, Maryland, for one year. In September, 1943, he entered Princeton University, from which institution he received the Bachelor of Arts degree in February, 1947. He enrolled in the Graduate College of the University of Illinois in September, 1947. He was the recipient of University fellowships during the academic years 1949-1950 and 1950-1951.

